

The purpose of this paper, however, is to show that a study of antitoxin in human serum supports for this one content our theory of individual variations.

In Chart 1 the plottings represent two groups, one of nineteen children, one to thirteen years, in whom antitoxin determinations were made six months after two doses of toxoid one-half and one cubic centimeter each, twenty-one days apart, had been given; and one of sixteen medical students, twenty-two to twenty-five years of age. This latter group were Schick-positive originally, then immunized with three doses of toxoid, 0.1, 0.2, and 0.3 cubic centimeter fourteen days apart. The antitoxin determinations and Schick tests were done six months after the immunizations. The children were all Schick-negative, but varied in antitoxin content from 1/25 to 4 units per cubic centimeter. Among the adults were four positive and twelve negative reactors with variations in antitoxin from less than 1/250 to 3 units per cubic centimeter. This latter group, having been chosen on the basis of a positive Schick, were more select than the children not so chosen. The level at which our skin tests were negative was between 1/200 and 1/100 unit. This figure is lower than the original of 1/30 unit per cubic centimeter, but is the level most other recent workers have found for a negative Schick. Some Schick-positive adults are very resistant to immunization, and interesting observations on them have been made, but that study is beyond the scope of this paper.

A longitudinal study of several individuals has been started. Determinations have been made at intervals throughout the past year. When the figures are plotted the curves tend to rise through the winter and spring months.

This rise, however, is not constant, but broken by many fluctuations. The cause of these fluctuations is not known. One reason for making this type of study of individuals was the hope that by repeated tests at short intervals we might be fortunate enough to pick up any sudden change in the amount of neutralizing substances, should such a change occur. There are many popular beliefs and considerable scientific literature on the subject of the effect of endocrines, vitamins, fatigue, illness, etc., on immunity. Even if changes occur, it obviously will be extremely difficult to interpret them without a vast amount of material. The field has unlimited problems for future exploration. Experimental evidence, however, does support the clinical observations that immunity is fluctuating and not static. Variations occur both in a cross section of the population and in a longitudinal study of individuals.

This method of studying immunity is crude. It measures rather roughly the neutralizing properties of serum for diphtheria toxin, but tells us nothing of the character of this substance or substances and nothing of cell immunity. Both the serum and cells are complicated structures which in physics and chemistry can be broken down into molecules, atoms, protons, etc. Each is a system as spacious in its own little self as is the solar system to us. Where in this structure then is immunity? The

patient can be bled and the immune properties are restored to the blood; cells are replaced after wear and tear by new ones that possess the same property. And yet, as noted above, immunity, as we know it, may suddenly disappear. To those who like to chase rainbows this intangible and capricious factor of life remains a fascinating subject.

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IDIOPATHIC ULCERATIVE COLITIS: THE EFFECTIVENESS OF LIVER EXTRACT IN ITS TREATMENT*

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DESPITE an intense interest in idiopathic ulcerative colitis, the etiology of this condition remains unknown. Consequently, the effectiveness of any form of treatment must be judged from clinical observation rather than scientific experimentation. In presenting a new form of treatment it is not only important to give the results obtained by this treatment, but also to review the probable causes of the disease and their theoretical relationship to the mode of therapy applied.

ETIOLOGY OF COLITIS: CURRENT VIEWS

At present the majority of the investigators studying ulcerative colitis believe it is primarily due to an infection involving the bowel mucosa. Evidence in favor of this has frequently been presented by Barger of the Mayo Clinic. No specific organism has been agreed upon, and vaccine and serum therapy have been most disappointing. In the past the cause has been vaguely designated as "diminished resistance" of the colon to infection, and recently Felsen¹ has emphasized that a previous attack of bacillary dysentery may make the bowel wall more susceptible to bacterial invasion. Diet and vitamin therapy, based on the lowered resistance hypothesis, have been equally disappointing. That some cases may be due to food allergy is now well recognized; but it is a rare case indeed in which the removal of some type of protein from the diet will produce a cure or even a satisfactory remission. An important and little-understood factor in causing ulcerative colitis is the effect of nervous-system influences on the activity of the colon. Nervous, highstrung patients may develop their attacks coincident with shock, great fatigue or prolonged nervous tension, and may develop remissions on sedative therapy alone. The effects of these four factors on the colon have been schematically presented in Figure 1. It is important to appreciate that one or more of these factors may contribute to the illness of any given patient, and that all of them must be considered in each individual.

LIVER THERAPY: RELATION TO ETIOLOGIC FACTORS

In what way could any beneficial effect of liver therapy be correlated with these etiologic factors?

* Read before the Section on General Medicine of the California Medical Association at the sixty-eighth annual session, Del Monte, May 1-4, 1939.

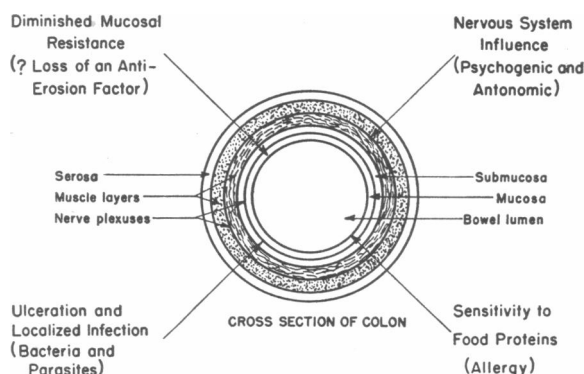


Fig. 1.—Diagram of the factors involved in the causation of ulcerative colitis.

It would not directly combat infection. It might well contain some as yet unidentified factor, possibly connected with the vitamin B complex, which would increase the resistance of the colonic mucosa to ulceration much in the same way that the chick antigizzard erosion factor will prevent or clear up superficial gastric ulcers in chicks.² The diminution or absence of such a factor may be the basic cause of the ulceration, and the other factors would then be only contributory. Untoward nervous-system influences on the colon might be alleviated in part at least by the vitamin B₁ content of liver, as has already been shown,³ but thiamin chlorid is not of prime importance in preventing ulceration.⁸ There is also some evidence accumulating to show that liver extract may contain some substance, probably vitamin B complex, which has to do with diminishing a patient's sensitivity to foreign proteins. On theoretical grounds, then, at least one might expect that liver therapy would be beneficial in treating idiopathic ulcerative colitis.

CLINICAL EVIDENCE

What clinical evidence is there that the administration of liver extract is of any value in the management of patients with ulcerative colitis? Up to the present time only a relatively small number of cases have been so treated, and the majority of these have shown very satisfactory improvement. It is the writer's belief that the analysis of a large number of records of patients with ulcerative colitis, for the purpose of establishing the benefits of a certain form of therapy, is of very little value compared to the careful personal observations of a small group of patients over a long period of time. Also there is only one form of the disease which lends itself well to a study of this sort, and that is the patient with chronic diarrhea which has persisted without remission for months or years. In patients with illness of short duration, or of the recurrent form when spontaneous remissions naturally occur, no evaluation of a particular form of treatment can be made without years of observation. In most of the large series of cases of ulcerative colitis which have been reported, detailed case observations have been lacking and the majority of the patients have apparently not been suffering chronically from constant diarrhea.

AUTHOR'S SERIES

In the writer's series of twenty-one cases treated with injections of liver extract which have already been reported,^{3,4} and in four other cases more recently observed over a period of six months or more, it has been possible to follow the majority of them with repeated observations as to the relationship of their therapy not only to their clinical manifestations, but also to their proctoscopic findings. All but three have been definitely benefited, and diarrhea has ceased entirely in twenty patients while maintained on adequate liver therapy. Nine of this group have been chronic sufferers from ulcerative colitis, and all but two have developed satisfactory remissions. It has been possible to stop treatment in this group and have relapses appear, and then resume treatment and have the symptoms clear up again. The improvement in some of these patients is almost as remarkable as that occurring in pernicious anemia treated with liver extract.

COMMENTS

Only parenteral liver extract has been used in treating these twenty-five cases, and it has usually been given in the concentrated form. Oral therapy is apparently not effective except in very rare instances. Ten to twenty U. S. P. units injected three times a week for the first two weeks, and then twice a week thereafter until a complete remission develops, has usually proved adequate. Maintenance therapy is essential to maintain good health. An injection of 20 U. S. P. units every one to three weeks is usually sufficient, but the necessary dose of liver extract will vary with the individual patient. Signs of improvement, such as diminution of the diarrhea, formed stools, increase in appetite and gain in weight, are usually noticeable by the third week of treatment, but may not be evident before the second month. There is no correlation between the severity of the disease and the time of response. Patients gravely ill may show early improvement, while ambulatory patients in good physical condition may not respond until after many weeks of injections. The only other forms of treatment usually employed besides the injection of liver extract are a high caloric, low residual diet, paregoric symptomatically, and bed rest for the acutely ill patient. Occasionally a vegetable muceloid or kaolin is given to solidify the stools during the early course of treatment. Rectal installations have been avoided.

Patients who do not seem to do well on liver-extract therapy must be carefully scrutinized to detect any factors which are acting as a barrier to their recovery, as concentrated liver-extract therapy alone may be ineffective. These factors are likely to fall into one or more of four categories:

First: The diagnosis may be incorrect: if the patient has diarrhea due to amebiasis, a remission is not likely to occur without administering an amebicide.

Second: The contributory factors of infection, allergy and nervous system instability already considered, may be of such importance as to nullify any beneficial effect of the liver. Patients with

high fever and leukocytosis and marked prostration who are not benefited by liver injections should be given a trial of neoprontosil, as the element of infection may so dominate the clinical picture that the bowel lesions cannot heal until this is overcome. Serum and vaccines have not proved helpful under these conditions—at least in the writer's experience. The question of food sensitivity is difficult to analyze; it must be given careful consideration in stubborn cases. The removal of a single offending protein food, such as milk, from the diet may make the difference between complete relief and interminable relapse. Probably the most difficult factor to combat is the over-excitability of the nervous system. Diarrhea as a manifestation of this condition is most troublesome to control, whether the bowel wall is ulcerated or not. Large doses of thiamin chlorid may be beneficial. Sedatives are often helpful. Failures with liver therapy are most likely to be in this group.

Third: The extent of the destructive process in the bowel wall must be considered. If the colon has become a narrowed, immobile tube, any improvement occurring will be slow and incomplete. The stools are likely to remain frequent in occurrence and unformed as the normal peristaltic and dehydration functions of the large bowel are lost. Patients with such damage to their colons cannot be expected to make a complete recovery on liver therapy, although the forward march of the pathologic process may be halted.

Fourth: The choice of liver extract may have an important bearing on the outcome of treatment. Up to the present time highly concentrated liver extract has been used. However, "highly concentrated" applies only to the anti-anemic substance, fraction G, and in liver extract so concentrated practically all of vitamin B₁ and B₂ are eliminated. It is not only probable that any substance effective in the treatment of ulcerative colitis may also be lost in the concentration process, but the administration of an unconcentrated liver solution parenterally to four cases recently indicates that it may be more effective than the concentrate. It was given intramuscularly in a dose of five cubic centimeters two or three times a week, representing only 5 U. S. P. units (anti-anemic) per dose.*

IN CONCLUSION

The effectiveness of liver extract in the treatment of idiopathic ulcerative colitis may best be summarized by stating that it is evidently beneficial in the majority of cases; in a few the results are truly brilliant, and in a few no definite benefit is obtained. In introducing a new form of therapy for any disease as uncontrollable as ulcerative colitis, overenthusiasm must be avoided, and failures, rather than condemning the treatment as a whole, must be extensively studied to ascertain the cause if possible. The probable reasons for such failures have been pointed out. As more cases are treated and our knowledge of this treatment is increased, not only may the results be improved, but the indications for success or failure may be

more clearly defined. When liver therapy was first shown to be effective in treating pernicious anemia, it was thought that all macrocytic hyperchromic anemias should respond. Gradually, over a period of years, it has been shown that many do not, because the mechanism of their production differs from that of pernicious anemia. In a like manner the future may show us that what we now call ulcerative colitis of unknown etiology represents different groups of cases varying in their basic etiology, and consequently in their response to liver therapy. At present all cases of idiopathic ulcerative colitis should be given a thorough, prolonged trial of parenteral liver treatment.

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EPIDERMOPHYTOSIS OF THE HANDS AND FEET: ITS TREATMENT*

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THIS much-discussed subject is interesting because the disease is so very prevalent and its various manifestations tax one's therapeutic resourcefulness more than most any other dermatological problem. The fact that there are recommended literally hundreds of remedies does not necessarily mean that none of them are effective, but rather is due to variations in the reactions of individuals to the infection and to the therapy applied. No attempt will be made here to cover all of the various methods of treatment, for it is hoped that this will be done by the discussants. One must be prepared to quickly modify the treatment to meet changing conditions. In my experience the results are much more satisfactory if the patient is seen often. During a week's absence from the office an application which helps at first may rapidly become irritating on account of some change in the host—due to foods, fatigue, or something else.

FACTORS TO BE CONSIDERED IN TREATMENT

First, one must consider the patient's general health, habits, and environment. Naturally a warm, moist skin that is not kept clean offers excellent soil for the growth of fungi. Where the sweat is more concentrated it has some fungicidal action, but where it is very dilute, as a result of excessive perspiration, this is absent. I have seen a long-standing fungus infection of one foot in a patient with acrodermatitis chronica atrophicans clear up

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* Horse liver extract may be more effective than beef liver extract.